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(57) Abstract

The present invention provides (i) a novel pharmaceutical composition comprising a synergistic combination of a non–digestible fructan–type carbohydrate, i.e. an inulin (including inulin, oligofructose and mixtures thereof) and an anti–metabolic anti–cancer drug, (ii) said composition for use in the treatment of cancer in humans and in non–ruminating mammals, (iii) the use of said combination for the manufacture of a medicament for the treatment of cancer in humans and in non–ruminating mammals, and (iv) the use of said composition in a method for treatment of cancer in humans and in non–ruminating mammals.

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SYNERGISTIC COMPOSITION FOR USE IN THE TREATMENT OF CANCER

Field of the invention

This invention relates to a pharmaceutical composition comprising a combination of a non-digestible carbohydrate and an anti-cancer drug , and to its use in the treatment of cancer in humans and in non-ruminating mammals.

Background and prior art

For various reasons, cancer has become one of the major causes of death of humans mainly in highly developed and highly industrialised countries.

Several kinds of cancer have already been identified. Although not all mechanisms of the carcino-genesis and development of all kinds of cancer have been elucidated so far, cancer is a disease which is known to proceed in several steps, conventionally including the stages of initiation, promotion and progression (Pitot, 1986). The initiation stage is characterised by a neoplastic modification of the genome in normal cells. In the promotion stage, the initiated cells with altered genome express their altered genome by a phenotypically detectable proliferation (premalignant foci, nodules or benign neoplasms). In the stage of progression, the benign neoplastic cells are transformed into malignant tumor cells proliferating in an uncontrolled manner, locally invading adjacent normal body tissues and organs and finally spreading into distant body tissues and organs by the metastases. The invasion of normal body structures usually results in their malfunctioning and destruction, which eventually results in the death of the affected human.

Cancer is also often seen in mammals in which the disease generally occurs through a mechanism similar to the one in humans.

On the one hand, various methods for the treatment of cancer have already been developed including treatment by surgery, by irradiation (X-rays, gamma rays, isotopes), by chemotherapy or, frequently, by combinations thereof.

The method of treatment of humans is commonly chosen taking into account *inter alia* the age and physical condition of the affected human and the kind, the location and the stage of development of the cancer. In a few

cases, the treatment will be effective and able to completely cure the affected person. In most cases, however, the treatment can only delay the carcinogenesis or more or less inhibit the development of the cancer disease and, in spite of bringing some temporary relief to the patient, the final outcome is unfortunately still fatal.

The treatment methods are continuously improving as a result of major research efforts. Invasive techniques, including surgery and irradiation, become more and more efficient as a result of technological developments, but require always more highly sophisticated equipment, making the techniques very costly and less suitable for large scale application. In the search to overcome the drawbacks of invasive treatments as well as for various other reasons, chemotherapy, in combination or not with other treatment methods, has become a major way of attack against cancer during the last two decades. A considerable advantage of anti-cancer drugs resides in the fact that they are easy to administer and current developments enable, in a steadily improving manner, target delivery of the drugs.

The anti-cancer drugs which have been developed are generally classified in one of the following groups:

1. alkylating agents, including e.g. cyclophosphamide (Endoxan®);
2. anti-metabolic drugs, including e.g. 5-fluorouracil and methotrexate;
3. anti-mitotic antibiotics, including e.g. doxorubicine and adriamycin;
4. alcaloidal anti-tumor agents, e.g. vincristine sulphate (Oncovin®);
5. hormones and antihormones,
6. interferons, e.g. alfa-2 b interferon; and
6. various anti-tumor agents,

as disclosed for example in the Répertoire commenté des médicaments, Ed. Centre Belge d'information pharmacothérapeutique, (1987), p. 341-345.

However, most of the anti-cancer drugs have serious disadvantages and drawbacks too. They may present a high degree of toxicity for cells of normal body structures causing, for example, liver and kidney damages. They may also cause an increased sensitivity to opportunistic infections. Often they also provoke various types of discomfort for the treated person, such as, local necrosis of the body structure in which the drug is parenterally administered, and, when the drug is administered orally or via tube feeding, nausea, vomiting, irritation of the mucoses of the digestive tract and diarrhoea. In addition to discomfort commonly caused by anti-cancer drugs, anti-metabolic anti-cancer drugs are known to be fairly toxic and to provoke

additional discomfort, including megaloblastose, and lesions to the liver or the digestive tract such as stomatitis and buccal and gastro-intestinal ulcers.

The disadvantages and drawbacks may considerably limit the use of available anti-cancer drugs. Indeed, often a curative effective dose of the drug can not be given to a patient due to the too high toxicity of the drug to normal cells or to the too high degree of discomfort caused to the patient by the drug.

On the other hand, beneficially inhibitory effects of certain dietary components on the incidence and growth of cancer have been disclosed *inter alia* by Williams and Dickerson (1990); Roberfroid (1991) and Milner (1994). Said components, termed functional food components (Roberfroid, 1995), may have almost no nutritional and/or caloric value but interact with physiological functions in the body in a manner to improve them or to restore them more or less in case of a disfunction.

Amongst the many dietary components, non-digestible carbohydrates, commonly termed dietary fibres, have been found to present preventive effects on carcinogenesis (Nossal, 1993; Perdigon et al.,1993) and possibly inhibitory effects on the promotion of carcinogenesis (Wattenberg, 1992).

Moreover, the relation between the intake of dietary fibres and the reduction of the risk of colon cancer has been disclosed in several publications, e.g. Potter et al., (1996); Howe et al., (1992) and Reddy et al., (1992).

Dietary fibres are commonly defined as components of plant cells which are resistant to hydrolysis by the alimentary enzymes of humans and non ruminating mammals. Dietary fibres comprise cellulose, hemi-cellulose, pectin, gums, waxes, lignin and certain other non-digestible carbohydrates.

Fructans are carbohydrates which are commonly classified in levans and inulins.

Levans are D-fructans generally consisting of water soluble chains of fructose units which are mostly connected to each other by ß(2-6) fructosyl-fructose linkages. Levans originate from the activity of certain bacteria and can be produced by known fermentation techniques as well as by enzymatic synthesis. Levans usually occur as a polydisperse mixture of polyfructose chains. These chains may be linear, but in general they are branched.

As ß(2-6) fructosyl-fructose linkages are not hydrolysed by alimentary enzymes in the upper part of the digestive tract of humans and non

ruminating mammals, levans pass almost unaltered into the colon where they are fermented by intestinal bacteria.

Inulins are D-fructans consisting of water soluble chains of fructose units too, but they are composed of chains in which the fructose units are connected to each other mostly or exclusively by ß(2-1) fructosyl-fructose linkages. Besides, inulin-type polyfructose chains often end in a glucose unit. Inulin mostly occurs as a polydisperse mixture of linear polyfructose molecules, as for example inulin from chicory, but inulin can also occur as a polydisperse mixture of branched polyfructose molecules, as for example inulin from dahlia and inulin from agave.

Inulins can be represented by the general formulae GF_n and F_n wherein G represents a glucosyl unit, F represents a fructosyl unit, and n represents the number of fructosyl units linked to each other in the carbohydrate chain. The number of saccharide units (fructose and glucose units) in one inulin molecule, *i.e.* the values n+1 in formula GFn and n in formula Fn, are referred to as the degree of polymerisation, represented by (DP). Often the parameter average degree of polymerisation of the inulin, represented by $(\overline{DP})$, is used too, which is the value corresponding to the total number of saccharide units divided by the total number of inulin molecules present in a given composition, without taking into account possibly present mono- and disaccharides (De Leenheer, 1996).

Inulins are synthesised by many plant species, in parts of which they may be stored as reserve carbohydrates, but inulins can also originate from bacterial activity and can be enzymatically synthesised as well. Inulin from plant origin is a polydisperse composition of polyfructose chains with a degree of polymerisation (DP) ranging from 3 to about 100, whereas inulin from bacterial origin usually has a higher (DP). The inulin profile, i.e. the distribution profile of the inulin chains according to their (DP), which to a certain extent is indicated by the average degree of polymerisation $(\overline{DP})$, depends from various factors, including the plant species, the time in the plant life cycle when the plant part is harvested, and the way the plant part is processed into inulin.

In roots of chicory, in tubers of dahlia and Jerusalem artichoke, and in the pinia of agave, inulin can occur at concentrations of about 10% to about 20 % on fresh weight. Inulin can be extracted easily from these plant parts, for example by extraction of the shredded plant parts with warm water. Then the crude inulin is purified and optionally fractionated to remove undesired fractions of carbohydrates. Finally, the inulin is isolated in

particulate form, usually by spray drying or by directed crystallisation. These different process steps are well known in the art. At industrial scale, inulin is mainly obtained from roots of chicory.

Inulin from chicory is commercially available in various grades, for example as RAFTILINE® from ORAFTI, (Tienen, Belgium). Typical RAFTILINE® grades are, for example , ST (which has a ($\overline{DP}$) of about 10 and contains in total about 8 % by weight glucose, fructose and sucrose), LS (which also has a ($\overline{DP}$) of about 10 but which contains in total less than 1 % by weight glucose, fructose and sucrose), and HP (which has a ($\overline{DP}$) $\geq$ 23, commonly a ($\overline{DP}$) of about 25 to about 30, and is essentially free of glucose, fructose and sucrose).

Inulin-type molecules of general formulae GF_n and F_n having a lower degree of polymerisation (DP), usually defined as a (DP) < 10, are often interchangeably termed oligofructoses, inulo-oligosaccharides and fructo-oligosaccharides, represented by FOS.

Unless specified otherwise, the term inulin herein is meant to comprise both inulin and oligofructose.

Oligofructose, which is thus an inulin of which the composing polyfructose chains have a (DP) < 10 , is usually obtained by partial, acidic or enzymatic hydrolysis of inulin, but can also be obtained by enzymatic synthesis from sucrose, according to techniques well-known in the art.

Several grades of oligofructose are commercially available, for example from ORAFTI (Tienen, Belgium) under the brand name RAFTILOSE®, for example, RAFTILOSE® P95 which contains about 95 % by weight oligofructose with a degree of polymerisation (DP) ranging from 2 to 7 and contains about 5 % by weight in total of glucose, fructose and sucrose.

Due to the presence of ß(2-1) fructosyl-fructose linkages between the fructosyl units of the inulin-type polyfructose chains, inulin is not digested by alimentary enzymes in the upper part of the digestive tract of humans and non ruminating mammals, but passes essentially unaltered into the lower part of the digestive tract to reach the colon where it is fermented by intestinal bacteria, while selectively promoting the growth of certain beneficial bacteria, particularly *Bifidobacteria* (Gibson et al., 1995). This bifidogenic effect, also called prebiotic effect, is known to exert beneficial effects on various physiological functions in the body.

In view of their almost non-digestibility by alimentary enzymes of humans and non ruminating mammals, fructans, levan-type fructans as

well as inulin-type fructans, are generally considered as soluble dietary fibres.

In patent application EP 97870069.8, the use has been described of fructan-type carbohydrates, particularly chicory inulin, with an average degree of polymerisation ($\overline{DP}$) of at least 15, for the manufacture of a composition for the prevention and treatment of colon cancer in non-bovine mammals, particularly in humans. Optionally, said composition can also comprise a physiologically active substance, a drug or pro-drug, but no particulars have been disclosed in this respect.

Furthermore, intraperitoneal injection of gamma-inulin, a specific polymorphic form of dahlia inulin, has been demonstrated to prolong the survival time of melanoma bearing mice (Cooper, 1986).

More recent studies revealed that non-digestible carbohydrates, including oligofructose and inulin, present inhibitory effects on the growth of intramuscularly transplanted mouse tumors (Taper et al., 1997).

Patent application EP 0 692 252 A1, discloses a composition containing inulin or oligofructose which presents a preventive effect on carcinogenesis and an inhibitory effect on the growth of cancer in mammals, particularly mammary cancer. EP 0 692 252 A1 also discloses compositions which in addition to inulin or oligofructose comprise conventional chemo-therapeutic products actively destroying malignant tumor cells. In this way, the combination of the physiologically beneficial effects of non-digestible carbohydrates and of the curative effects of anti-cancer drugs are sought. Furthermore, in Example 7 (page 12 of EP 0 692 252 A1) is mentioned that to determine potential synergistic therapeutic effects, a pharmaceutical composition comprising RAFTILINE® (i.e. chicory inulin) and a conventional chemotherapeutic product actively destroying malignant tumor cells, is prepared and a test is described wherein doxorubicine (an anti-cancer drug of the class of the antimitotic antibiotics) was injected to mice fed oligofructose/RAFTILINE® which were previously inoculated with L1210 leukaemic tumor cells. However, EP 0 692 252 A1 is completely silent about the outcome of the test and about possible synergistic effects between a non-digestible fructan-type carbohydrate and conventional anti-cancer drugs.

The combined effect of levan and four cytotoxic agents on the growth of experimental tumors in mice has been published (Leibovici et al., 1983). Additive effects were observed with all the combinations of levan and the cytotoxic agents, except for the combination of levan and methotrexate, an

anti-metabolite anti-cancer agent, which gave a synergistic effect on Lewis lung carcinoma. However, no synergistic effect was observed for the combination of levan and 5-fluorouracil, an other anti-metabolite anti-cancer drug.

The problem

In view of the tremendous social and economical impact of cancer on individuals as well as on society in general, huge efforts are continuously made world-wide to find new or improved products, compositions and methods for the treatment of cancer. In particular, the search is continued in order to find highly effective drugs, preferably with a low degree of toxicity to normal cells, and compositions thereof, which are providing good therapeutic effects while provoking minimal discomfort to the patient.

Description of the invention

The present invention provides a solution to one or more of the problems mentioned above, by providing (i) a novel pharmaceutical composition comprising a synergistic combination of a non-digestible carbohydrate, i.e. an inulin (including inulin, oligofructose and mixtures thereof) and an anti-cancer drug , (ii) said composition for use in the treatment of cancer in humans and in non-ruminating mammals, (iii) the use of said combination for the manufacture of a medicament for the treatment of cancer in humans and in non-ruminating mammals, and (iv) the use of said composition in a method for treatment of cancer in humans and in non-ruminating mammals.

By the term cancer is meant herein any kind of cancer occurring in humans and in non-ruminating mammals, irrespective of the stage of development of said cancer, thus including, in particular, the initiation, promotion, progression stages and the metastasis stage.

The invention is based on the findings made by the inventors that the combination of inulin and an anti-metabolic anti-cancer drug, not only results in an additive therapeutical effect vis-à-vis the carcinogenesis and the growth of cancer in humans and in non-ruminating mammals, but surprisingly provokes a synergistic therapeutical effect vis-à-vis said disease.

So, in one aspect the present invention relates to a novel pharmaceutical composition comprising a synergistic combination of inulin and an anti-metabolic anti-cancer drug , which combination provokes a

synergistic therapeutical effect on the carcinogenesis and growth of cancer in humans and in non-ruminating mammals.

Typically suitable inulins include chicory inulin, in particular, inulin with a ($\overline{DP}$) of about 10, such as for example RAFTILINE® ST and RAFTILINE® LS, and inulin with a ($\overline{DP}$) ≥ 23, such as, for example, RAFTILINE® HP and a suitable oligofructose is, for example, RAFTILOSE® P95, all from ORAFTI (Belgium).

The term therapeutical effect used herein refers to an inhibitory effect on the incidence and growth of cancer as well as to a curative effect provoking the decrease of the volume of an existing cancer and possibly the regression or curing of the cancer disease.

By anti-metabolic anti-cancer drug is meant a drug selected from said class of anti-cancer drugs which embraces products which compete with the normal metabolites of nucleic acids in cell synthesis and in cell growth pathways. This class of drugs is comprising methotrexate, cytarabin, fluorouracil, mercaptopurin, thioguanine, azathioprin and hydroxy-carbamide.

It is understood that the term drug used herein includes the drug *per se* as well as a pro-drug, i.e. a compound which in the body is transformed into the corresponding drug.

The composition according to the invention is suitable in the first place for the treatment of cancer in humans. However, it is very suitable too for the treatment of cancer in non-ruminant mammals, such as for example horses, rabbits, dogs and cats.

In a preferred embodiment the inulin is a chicory inulin with a ($\overline{DP}$) of about 10. In another preferred embodiment the inulin is a chicory inulin with a ($\overline{DP}$) of ≥ 23, typically of about 25 to about 30. In still another preferred embodiment, the inulin is an oligofructose, more preferably an oligofructose with a (DP) of 2 to 7.

In a further preferred embodiment, the anti-metabolic drug is 5-fluorouracil or methotrexate.

In a particularly preferred embodiment the inulin is chicory inulin or oligofructose or a mixture thereof and the anti-cancer drug is 5-fluorouracil or methotrexate.

Furthermore, a composition according to the present invention may comprise, instead of one anti-metabolic drug, a mixture of two or more anti-metabolic drugs as well as a mixture of one or more anti-metabolic drugs with one or more anti-cancer drugs belonging to a different class.

The composition according to the invention can be prepared by conventional methods, comprising, for example, mixing the desired amounts of the active components, optionally in combination with one or more pharmaceutically acceptable solvents, diluents, excipients, and/or additives commonly used in galenic pharmacy.

The compositions can be presented in conventional, well known galenic forms for oral, parenteral or rectal administration, or for tube feeding. The compositions for oral administration can for example be liquids, gels or solids and exist, for example, as tablets, coated tablets, coated pills, capsules, granules, solutions, syrups, suspensions or emulsions. The compositions for administration via tube feeding can for example be solutions, syrups, suspensions or emulsions which optionally can be mixed with normal food compositions for tube feeding. The compositions for rectal administration may for example be solids, gels or liquids, presented for example in the form of suppositories, gels, solutions, suspensions or emulsions. The composition for parenteral administration can for example be in the form of a solution, emulsion or suspension, suitable for said administration, including for subcutaneous, intramuscular, intraveneous and intraperitoneal administration.

Suitable galenic forms also include retard release forms as well as sustained release forms which are well known in the art.

The composition according to the invention comprises at least an active dose of the inulin as well as of the anti-cancer drug or drug mixture. A dose which is effective for treatment of cancer can be formulated in the form of a single dose unit or of several partial dose units, the administration of which can be spread over a certain period of time. Usually the composition according to the invention will be administered spread over several partial dose units, and spread, possibly with certain intervals, over one or more days or weeks.

The effective dose of the synergistic combination of inulin and anti-metabolic anti-cancer drug may depend on various factors, including the affected being, a human or species of non-ruminating mammals, its age and physical condition, the kind and stage of development of the cancer, the kind of inulin and of anti-cancer drug, and the method of administration of the synergistic combination. The effective dose, the optimal galenic form and unit dose, and the way of administration can be determined by the skilled person following conventional methods.

A particularly interesting feature of the compositions according to the invention resides in the fact that the active ingredients of the synergistic combination, i.e. the inulin and the anti-metabolic anti-cancer drug, can be administered to the human or non ruminating mammal (i) simultaneously and present in the same galenical formulation (constituting the pharmaceutical composition according to the present invention) , or (ii) simultaneously but present in two separate galenic formulations (constituting together the pharmaceutical composition according to the present invention) and optionally via two different methods of administration, as well as (iii) separately, i.e. non simultaneously, via two separate galenic formulations (constituting together the pharmaceutical composition according to the present invention) and optionally via two different methods of administration.

It is understood that in the above mentioned methods of administration, the inulin component as well as the anti-cancer drug of the composition of the invention, can be administered orally, via tube feeding, parenterally or rectally.

Furthermore, the combined composition or each of the active components can be administered locally or systemically, and they, accordingly, have to be present in a galenic formulation which is suitable for the method of administration.

When the fructan component and the anti-cancer drug component of the combination according to the invention are not simultaneously administered to the human or mammal, it is of course compulsory that they are brought into the body of said being in such a manner that their functional effects on the human or mammal are simultaneously present in order to provoke the synergistic effect in accordance with the present invention.

According to one preferred embodiment, both active ingredients are administered simultaneously in one pharmaceutical composition to the human or mammal.

In an other preferred embodiment, both active ingredients are administered simultaneously but in separate formulations. Optionally a different way of administration for each of the formulations can be used.

In a further preferred embodiment both active ingredients are administered separately in separate formulations and optionally via different methods of administration and/or at different time periods.

If the active ingredients are not administered simultaneously via the same formulation, the anti-cancer drug is preferably administered orally or parenterally, whereas the inulin is preferably administered orally, via tube feeding or parenterally. The inulin can be administered in various galenic formulations, such as for example tablets, capsules, syrups, solutions, suspensions or emulsions. The inulin can even be administered orally in the form of a functional food or feed, i.e. a food or feed product which during its manufacture has been provided with the desired amount of inulin, such as, for example, dairy products e.g. yoghurts or cheeses; jams or marmalades; baked goods e.g. biscuits, breads or breakfast cereals; desserts e.g. puddings or ice-creams; table spreads, e.g. margarines; drinks; meal replacers; or confectionery, e.g. gums.

In a further preferred embodiment, inulin is already administered to the human or mammal some time, for example one week, before the composition of the invention is administered. Without wishing to be bound by any theory, it is supposed that as a result of the bifidogenic effect of the previously administered inulin, the intestinal flora and/or the effected functions have been brought into a condition in which the synergistic effect provoked by the combination of active ingredients according to the invention can develop optimally.

In a further aspect the invention relates to a pharmaceutical composition as defined herein above for the treatment of cancer in humans or in non-ruminating mammals.

In still a further aspect, the invention relates to the use of a combination of inulin and an anti-metabolic anti-cancer drug for the manufacture of a pharmaceutical composition as defined herein above for the treatment of cancer in humans or in non-ruminating mammals.

In still another aspect, the invention relates to a method for the treatment of cancer in humans or in non-ruminating mammals, comprising administering to said being in need for such treatment an effective dose of the pharmaceutical composition comprising a synergistic combination of inulin and an anti-metabolic anti-cancer drug as defined above, said active ingredients, i.e. the inulin and the anti-cancer drug, being administered either simultaneously in the same or in separate formulations, or non-simultaneously in separate formulations and optionally after previous administration of inulin during a certain period, as described herein before.

Examples

In support of the present invention, the following illustrative data are given regarding experiments wherein the therapeutical effects on cancer in mice of a composition according to the present invention are compared with the therapeutical effects of a composition containing a combination of inulin with an anti-cancer drug which belongs to a different class.

To investigate whether dietary treatment with inulin (inulin or oligofructose [FOS]) would be able to potentiate the therapeutic effects of anti-cancer drugs commonly utilised in human cancer treatment, representatives of 4 principal classes of anti-cancer drugs have been chosen and compared in the following test.

The drugs were: endoxan (belonging to the class of alkylating agents), adriblastina (adriamycin) (belonging to the class of antimitotic antibiotics), 5-fluorouracil (belonging to the class of anti-metabolic agents) and oncovin (belonging to the class of antineoplastic alkaloids).

Viable, neoplastic cells (10^6) from the ascitic form of a transplantable mouse liver tumor (TLT) (Taper, 1966 and Cappucino, 1966) were intraperitoneally transplanted into 12 per group young adult NMRI male mice weighing about 30 g, supplied by "Animalerie Facultaire", UCL, Brussels. Mice of the experimental groups were fed with a basal diet supplemented with 15 % FOS or inulin starting 7 days before tumor transplantation up to the end of the experiment. Control animals received the basal diet for experimental animals AO4 furnished by UAR, Villemoisson sur Orge, France, and water ad libitum.

A single, subtherapeutic dose of cytotoxic drugs was intraperitoneally injected 48 hours after intraperitoneal TLT tumor transplantation at following doses: endoxan 80 mg/kg; adriamycin 0.1 mg/kg; oncovin 0.5 mg/kg and 5-fluorouracil 40 mg/kg.

The criteria for the evaluation of results were the mortality rates expressed by mean survival time (MST) and the percentage of increase of life span (ILS) in experimental groups compared with the controls, calculated according to the NCI instructions (Geron et al., 1972). The results of each experiment were confirmed by another experiment performed at another time and were cumulatively calculated (as presented in Table 1).

The results concerning the survival rates of mice bearing the ascitic form of a TLT tumor, observed in 2 separately performed experiments on each type of anti-cancer drug (12 mice per group), are cumulatively presented in Table 1 below.

In all the experiments a chemotherapy potentiating effect has been observed for dietary FOS or inulin. Obviously this therapeutic effect was somewhat different for the various drugs. Only for 5-fluorouracil treatment a synergistic therapeutic effect has bee observed. For treatment with oncovin, endoxan and adriamycin, the therapeutic effects had only additive character. There is no significant difference observed between treatment with inulin or FOS.

All results of supplementary dietary FOS treatment were statistically very highly significant ($p < 0.001$). There were no negative results in any of the separately performed experiments. `Furthermore, no gastro-intestinal troubles were observed in all animals after the direct introduction of 15 % FOS or inulin in the diet. There was no sign of increased drug toxicity after dietary introduction of both inulin or FOS (e.g. there was no difference in body weights between mice treated only with a cytotoxic drug and those treated with supplementary inulin or FOS).

Furthermore, it should be noted that in the experiments unfavourably therapeutic conditions were deliberately utilised by the administration of a single, sub-therapeutic dose of cytotoxic drug 48 hours after the intra-peritoneal transplantation of a very aggressive and rapidly growing ascitic form of mouse tumor.

In a further experiment, carried out in a similar manner as the previous experiment, the effects were examined of a composition according to the invention, containing a combination of the anti-metabolite anti-cancer drug methotrexate and inulin or FOS, in comparison with the effects of the single components.

The effects were evaluated via the survival criteria of N.M.RI mice bearing ascitic TLT tumors, treated with a single i.p. dose of 20 mg/kg methotrexate (10 investigated mice in each group) and the results are presented in Table 2 below.

TABLE 1.

Therapeutic effects of FOS or inulin associated to a single dose of different cytotoxic drugs administered to ascitic TLT tumor bearing mice

Treatment	ILS (%)	Effect of combined treatment	Statistical significance
5-Fluorouracil *	18.75		
FOS *	12.5		
5-Fluorouracil + FOS	40.6	Synergistic	$p < 0.001$
Adriamycin *	14.7		
FOS *	5.9		
Adriamycin + FOS *	17.6	Additive	$p < 0.001$
Endoxan *	0		
FOS *	25.0		
Endoxan + FOS *	25.0	Additive	$p < 0.001$
Oncovin *	33.33		
FOS *	13.33		
Inulin *	10.0		
Oncovin + FOS *	46.66	Additive	$p < 0.001$
Oncovin + Inulin *	43.33	Additive	$p < 0.01$

Each of the differently treated group of 12 mice had its individual, untreated, control group to which it was compared in the calculation of the increase of life span (ILS). The cumulatively presented results are based each on 2 experiments independently performed at different time. Lagrank test was utilised for statistical analysis of the results.

*: comparative test

TABLE 2.

Therapeutic effects of FOS or inulin associated to a single dose of methotrexate administered i.p. at 20 mg/kg to ascitic TLT tumor bearing mice

Treatment	ILS (%)	Effect of combined treatment
untreated (control) *		
methotrexate *	2	
FOS *	5	
inulin *	11	
methotrexate + FOS	29	Synergistic
methotrexate + inulin	20.5	Synergistic

*: comparative test

From the comparative data presented in Tables 1 and 2, it clearly follows that the composition according to the present invention comprising a combination of inulin and an anti-metabolic anti-cancer drug has a synergistic therapeutical effect on cancer in mice, whereas for the compositions containing inulin and an anti-cancer drug of an other class only an additive effect is observed. Besides, the compositions of the invention provoked no disadvantageous effects on the digestive tract and were not potentiating the toxicity of the anti-cancer drug.

As a result of said synergistic effect the compositions of the invention present considerable advantages over conventional anti-cancer compositions. For example, compared to a conventional composition containing the same concentration of anti-cancer drug, the therapeutical effect of a composition of the invention is significantly increased which may lead to a considerable improvement of the bodily condition of the treated human or mammal and which may enable to better control the disease and even enable to have restored to a more or lesser extent the normal physiological functions and affected body structures. On the other hand, said synergistic effect can enable the use of certain anti-cancer drugs, which are fairly toxic or provoke disadvantageous side effects, in compositions according to the invention in reduced concentrations while still maintaining the same or a desirable level of therapeutical effect. Said synergistic effect makes it even possible to use certain anti-cancer drugs which, at the concentration they have to be used in conventional composition to obtain a desired therapeutical effect, are too toxic or provoke such undesirable side effects that they can not be supported by the treated human or mammal.

In addition, the treated human or mammal also enjoys the known beneficial effects resulting from the bifidogenic effect of the inulin which is present in the composition of the invention.

Consequently, it can be concluded that the composition and method according to the invention present a considerable improvement in the fight against cancer in humans and in non-ruminating mammals.

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Claims

1. Pharmaceutical composition comprising a synergistic combination of inulin and an anti-metabolic anti-cancer drug.

2. Pharmaceutical composition according to claim 1 wherein the inulin is inulin with a DP up to about 100, or oligofructose or a mixture thereof.

3. Pharmaceutical composition according to claim 1 or claim 2, wherein the inulin is chicory inulin with a ($\overline{DP}$) ranging from about 10 to about 30, or oligofructose with a DP ranging from 2 to 7 and containing about 5 wt% in total of glucose, fructose and sucrose.

4. Pharmaceutical composition according to any one of claims 1 to 3 wherein the anti-cancer drug is selected from the group consisting of methotrexate, cytarabin, fluorouracil, mercaptopurin, thioguanin, azathioprin and hydroxycarbamide.

5. Pharmaceutical composition according to claim 4 wherein the anti-cancer drug is 5-fluorouracil or methotrexate.

6. Pharmaceutical composition according to any one of claims 1 to 5 which additionally to the said anti-metabolic anti-cancer drug contains one or more anti-cancer drugs belonging to the class of anti-metabolic anti-cancer drugs and/or to another class of anti-cancer drugs.

7. Pharmaceutical composition according to any one of claims 1 to 6 in which the inulin and the anti-metabolic anti-cancer drug which constitute the synergistic combination are simultaneously present in the same galenic formulation.

8. Pharmaceutical composition according to any one of claims 1 to 6 in which the inulin and the anti-metabolic anti-cancer drug which constitute the synergistic combination are present in separate formulations which together form the pharmaceutical composition.

9. Pharmaceutical composition according to any one of claims 1 to 8 wherein the single galenic formulation or the separate galenic formulations forming the pharmaceutical composition are suitable for oral, parenteral or rectal administration, or for tube feeding.

10. Pharmaceutical composition according to claim 8 in which the inlin is present in a functional food or feed.

11. Pharmaceutical composition according to claim 8 in which the anti-cancer drug is present in a formulation which is suitable for oral or parenteral administration.

12. Pharmaceutical composition according to any one of claims 1 to 11 for use as a medicament for the treatment of cancer in humans.

13. Pharmaceutical composition according to any one of claims 1 to 11 for use as a medicament for the treatment of cancer in non-ruminating mammals.

14. Use of a combination of inulin and an anti-metabolic anti-cancer drug for the manufacture of a pharmaceutical composition as defined in any one of claims 1 to 11 for the treatment of cancer in humans or in a non-ruminating mammal.

15. Method for the treatment of cancer in a human or in a non-ruminating mammal comprising administering to said being in need of such treatment an effective amount of a pharmaceutical composition as defined in any one of claims 1 to 11.

16. Method according to claim 15 wherein the inulin and the anti-metabolic anti-cancer drug of the synergistic combination forming the composition are present in the same galenic formulation constituting the pharmaceutical composition.

17. Method according to claim 15 wherein the inulin and the anti-metabolic anti-cancer drug of the synergistic combination forming the pharmaceutical composition are present in separate galenic formulations constituting together the pharmaceutical composition.

18. Method according to claim 17 wherein the separate galenic formulations are administered simultaneously or non-simultaneously.

19. Method according to claim 17 wherein the separate galenic formulations are administered via different methods of administration and the inulin is administered by a method selected from the group consisting of oral, parenteral or rectal administration and administration via tube feeding.

20. Method according to claim 19 wherein the separate galenic formulation containing the inulin is a functional food or feed.

INTERNATIONAL SEARCH REPORT

Ir ıational application No.
PCT/EP 99/03399

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 15-20
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 15-20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Intern· ·nal Application No
PCT/EP 99/03399

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/70 A61K31/505 A61K31/52 A61K31/17 A61K31/715

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 692 252 A (RAFFINERIE TIRLEMONTOISE SA) 17 January 1996 (1996-01-17) cited in the application page 2, line 49 -page 3, line 29 ---	1-20
A	LEIBOVICI J. ET AL: "Combined effect of levan and cytotoxic agents on the growth of experimental tumours in mice" BR. J. EXP. PATHOL., 1983, 64/3 (239-244), XP002083711 ENGLAND cited in the application abstract -----	1-20

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 October 1999	05/11/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Leherte, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

ormation on patent family members

Intern· nal Application No
PCT/EP 99/03399

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0692252 A	17-01-1996	US 5721345 A	24-02-1998

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No. PCT/EP99/03399

International Filing Date (18 05 1999) 18 MAY 1999

EUROPEAN PATENT OFFICE
PCT INTERNATIONAL APPLICATION

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* PRAFF 28/WO

Box No. I TITLE OF INVENTION

Synergistic composition for use in the treatment of cancer

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

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Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

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Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

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Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

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State *(that is, country)* of nationality: BE

State *(that is, country)* of residence: BE

This person is applicant for the purposes of:
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- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

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Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

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- ☒ EP **European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
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- ☐ **LR** Liberia
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- ☐ .....
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Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 18 May 1998 (18.05.1998)	98870113.2		EP	
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): (1)

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):*
ISA / EP

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*

Date (day/month/year)	Number	Country (or regional Office)
9 November 1998 (09.11.1998)	98870113.2	EP

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets:**

request	:	4
description (excluding sequence listing part)	:	17
claims	:	2
abstract	:	1
drawings	:	0
sequence listing part of description	:	0
Total number of sheets	:	24

This international application is **accompanied by** the item(s) marked below:

1. ☒ fee calculation sheet
2. ☒ separate signed power of attorney (2 forms)
3. ☒ copy of general power of attorney; reference number, if any: 38099
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☒ other *(specify)*: European Search Report of EP98870113.2

Figure of the drawings which should accompany the abstract: -

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

HERMANS Johny
Agent; European Patent Attorney N° 85220

For receiving Office use only

1. Date of actual receipt of the purported international application:	(18.05.1999) 18 MAY 1999	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:		
4. Date of timely receipt of the required corrections under PCT Article 11(2):		
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid.	

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ EP

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference: PRAFF 28/WO

International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/EP99/03399	18 May 1999 (18.05.99)	18 May 1998 (18.05.98)

Title of invention: Synergistic composition for use in the treatment of cancer.

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

TIENSE SUIKERRAFFINADERIJ N.V.
Tervurenlaan 182
B-1150 Brussel
Belgium

Telephone No.: 32-(0)2-775.80.20
Facsimile No.:
Teleprinter No.:

State *(that is, country)* of nationality: BE
State *(that is, country)* of residence: BE

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TAPER Henryk
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FRIPPIAT Anne
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State *(that is, country)* of residence: BE

[X] Further applicants are indicated on a continuation sheet.

International application No.
PCT/EP99/03399

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

VAN LOO Jan
Lepelstraat 3
B-3000 Leuven
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ROBERFROID Marcel
Rue du Coq 71
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Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

☐ Further applicants are indicated on another continuation sheet.

International application No.
PCT/EP99/03399

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is [X] agent [ ] common representative

and [X] has been appointed earlier and represents the applicant(s) also for international preliminary examination.

[ ] is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

[ ] is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

HERMANS Johny
Tiense Suikerraffinaderij N.V.
Aandorenstraat 1
B-3300 Tienen (Belgium)

Telephone No.: 32-(0)16.80.12.92

Facsimile No.: 32-(0)16.80.13.59

Teleprinter No.:

[ ] **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination **to start on the basis of:**

[X] the international application as originally filed

the description [X] as originally filed
[ ] as amended under Article 34

the claims [X] as originally filed
[ ] as amended under Article 19 (together with any accompanying statement)
[ ] as amended under Article 34

the drawings [ ] as originally filed
[ ] as amended under Article 34

2. [ ] The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. [ ] The applicant wishes the start of the international preliminary examination **to be postponed** until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

[X] which is the language in which the international application was filed.

[ ] which is the language of a translation furnished for the purposes of international search.

[ ] which is the language of publication of the international application.

[ ] which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby **elects all eligible States** *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes **not to elect:**

Sheet No. 4.

International application No.
PCT/EP99/03399

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

			For International Preliminary Examining Authority use only	
			received	not received
1. translation of international application	:	sheets	☐	☐
2. amendments under Article 34	:	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:	sheets	☐	☐
5. letter	:	sheets	☐	☐
6. other *(specify)*	:	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. [X] fee calculation sheet
2. [ ] separate signed power of attorney
3. [ ] copy of general power of attorney; reference number, if any:
4. [ ] statement explaining lack of signature
5. [ ] nucleotide and or amino acid sequence listing in computer readable form
6. [ ] other *(specify)*:

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

November 18. 1999

HERMANS Johny
Applications' Agent
European Patent Attorney

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:
2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):
3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

CHAPTER II

PCT

FEE CALCULATION SHEET

Annex to the Demand for international preliminary examination

International application No. PCT/EP99/03399	For International Preliminary Examining Authority use only
Applicant's or agent's file reference PRAFF 28/WO	Date stamp of the IPEA
Applicant: Tiense Suikerraffinaderij N.V. et al.	

Calculation of prescribed fees

1. Preliminary examination fee	DEM 2.998,29	P
2. Handling fee *(Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)*	DEM 289,46	H
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	DEM 3.287,75 TOTAL	

Mode of Payment

[X]	authorization to charge deposit account with the IPEA (see below)	[ ]	cash
[ ]	cheque	[ ]	revenue stamps
[ ]	postal money order	[ ]	coupons
[ ]	bank draft	[ ]	other *(specify)*:

Deposit Account Authorization *(this mode of payment may not be available at all IPEAs)*

The IPEA/ EP [X] is hereby authorized to charge the total fees indicated above to my deposit account.

[X] *(this check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)* is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

28020058	18 November 1999 (18.11.99)	HERMANS Johny
Deposit Account Number	Date *(day/month/year)*	Signature

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PRAFF 28/WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/03399	18/05/1999	18/05/1998
International Patent Classification (IPC) or national classification and IPC A61K31/70		
Applicant TIENSE SUIKERRAFFINADERIJ N.V.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19/11/1999	14.08.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Simm, M.D. Telephone No. +49 89 2399 7411

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/03399

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-5,7,8,10-17	as originally filed			
6,9	as received on	12/05/2000	with letter of	11/05/2000

Claims, No.:

1-20	as received on	12/05/2000	with letter of	11/05/2000

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 15-20.

because:

☒ the said international application, or the said claims Nos. 15-20 in respect of i.a. relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-20
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-20
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	15-20

2. Citations and explanations

see separate sheet

Re Item I

Basis of the report

D1: EP-A-0 692 252 (RAFFINERIE TIRLEMONTOISE SA) 17 January 1996 (1996-01-17) cited in the application

D2: LEIBOVICI J. ET AL: 'Combined effect of levan and cytotoxic agents on the growth of experimental tumours in mice' BR. J. EXP. PATHOL., 1983, 64/3 (239-244), XP002083711 ENGLAND cited in the application

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 15-20 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Novelty (Art. 33(2) PCT)

D1 discloses the combination of inulin with anti-cancer drugs, among them the group of antimetabolites is listed on page 3 in the description of D1.
The combination of inulin with an anti-metabolic anti-cancer drug claimed in the present application represents the selection of a sub-range of compounds from a broader known range, namely the one of the whole anti-cancer drugs. Such a selected sub-range is considered to be novel if it is narrow compared to the known range and includes a new technical teaching. These two criteria are met in the present case because of the synergistic effect shown between inulin and anti-metabolic anti-cancer

drugs, which D1 fails to show, and because the group is much narrower than the one of the whole anti-cancer drugs.

Inventive Step (Art. 33(3) PCT)

D2 discloses the synergistic effect between levans and methotrexate, which is an anti-metabolic anti-cancer. However, the combination levans with 5-Fluorouracil, another anti-metabolic anti-cancer, shows just an additive effect. In addition the document does not mention inulin. Even considering that levans and inulins are equivalent compounds and therefore the substitution of levans for inulin is obvious, D2 fails to predict the synergistic effect shown in the present application.

Thus, the invention claimed is not rendered obvious in view of the prior art and claims 1-20 appear to involve an inventive step over the prior art.

Industrial Applicability (Art. 33(4) PCT)

For the assessment of the present claims 1-14 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Claims

1. Pharmaceutical composition characterised in that it comprises a ~~comprising a synergistic~~ combination of an effective dose of inulin and an effective dose of an anti-metabolic anti-cancer drug.

2. Pharmaceutical composition according to claim 1 wherein the inulin is inulin with a DP up to about 100, or oligofructose or a mixture thereof.

3. Pharmaceutical composition according to claim 1 or claim 2, wherein the inulin is chicory inulin with a ($\overline{DP}$) ranging from about 10 to about 30, or oligofructose with a DP ranging from 2 to 7 and containing about 5 wt% in total of glucose, fructose and sucrose.

4. Pharmaceutical composition according to any one of claims 1 to 3 wherein the anti-cancer drug is selected from the group consisting of methotrexate, cytarabin, fluorouracil, mercaptopurin, thioguanin, azathioprin and hydroxycarbamide.

5. Pharmaceutical composition according to claim 4 wherein the anti-cancer drug is 5-fluorouracil or methotrexate.

6. Pharmaceutical composition according to any one of claims 1 to 5 which additionally to the said anti-metabolic anti-cancer drug contains one or more anti-cancer drugs belonging to the class of anti-metabolic anti-cancer drugs and/or to another class of anti-cancer drugs.

7. Pharmaceutical composition according to any one of claims 1 to 6 in which the inulin and the anti-metabolic anti-cancer drug which constitute the ~~synergistic~~ combination are simultaneously present in the same galenic formulation.

8. Pharmaceutical composition according to any one of claims 1 to 6 in which the inulin and the anti-metabolic anti-cancer drug which constitute the ~~synergistic~~ combination are present in separate formulations which together form the pharmaceutical composition.

9. Pharmaceutical composition according to any one of claims 1 to 8 wherein the single galenic formulation or the separate galenic formulations forming the pharmaceutical composition are suitable for oral, parenteral or rectal administration, or for tube feeding.

10. Pharmaceutical composition according to claim 8 in which the inlin is present in a functional food or feed.

11. Pharmaceutical composition according to claim 8 in which the anti-cancer drug is present in a formulation which is suitable for oral or parenteral administration.

12. Pharmaceutical composition according to any one of claims 1 to 11 for use as a medicament for the treatment of cancer in humans.

13. Pharmaceutical composition according to any one of claims 1 to 11 for use as a medicament for the treatment of cancer in non-ruminating mammals.

14. Use of a combination of inulin and an anti-metabolic anti-cancer drug for the manufacture of a pharmaceutical composition as defined in any one of claims 1 to 11 for the treatment of cancer in humans or in a non-ruminating mammal.

15. Method for the treatment of cancer in a human or in a non-ruminating mammal comprising administering to said being in need of such treatment an effective amount of a pharmaceutical composition as defined in any one of claims 1 to 11.

16. Method according to claim 15 wherein the inulin and the anti-metabolic anti-cancer drug of the ~~synergistic~~ combination forming the pharmaceutical composition are present in the same galenic formulation constituting the pharmaceutical composition.

17. Method according to claim 15 wherein the inulin and the anti-metabolic anti-cancer drug of the ~~synergistic~~ combination forming the pharmaceutical composition are present in separate galenic formulations constituting together the pharmaceutical composition.

18. Method according to claim 17 wherein the separate galenic formulations are administered simultaneously or non-simultaneously.

19. Method according to claim 17 wherein the separate galenic formulations are administered via different methods of administration and the inulin is administered by a method selected from the group consisting of oral, parenteral or rectal administration and administration via tube feeding.

20. Method according to claim 19 wherein the separate galenic formulation containing the inulin is a functional food or feed.

well as inulin-type fructans, are generally considered as soluble dietary fibres.

In patent application EP 0 879 600, ~~EP 97870069.8~~, the use has been described of fructan-type carbohydrates, particularly chicory inulin, with an average degree of polymerisation ($\overline{DP}$) of at least 15, for the manufacture of a composition for the prevention and treatment of colon cancer in non-bovine mammals, particularly in humans. Optionally, said composition can also comprise a physiologically active substance, a drug or pro-drug, but no particulars have been disclosed in this respect.

Furthermore, intraperitoneal injection of gamma-inulin, a specific polymorphic form of dahlia inulin, has been demonstrated to prolong the survival time of melanoma bearing mice (Cooper, 1986).

More recent studies revealed that non-digestible carbohydrates, including oligofructose and inulin, present inhibitory effects on the growth of intramuscularly transplanted mouse tumors (Taper et al., 1997).

Patent application EP 0 692 252 A1, discloses a composition containing inulin or oligofructose which presents a preventive effect on carcinogenesis and an inhibitory effect on the growth of cancer in mammals, particularly mammary cancer. EP 0 692 252 A1 also discloses compositions which in addition to inulin or oligofructose comprise conventional chemo-therapeutic products actively destroying malignant tumor cells. In this way, the combination of the physiologically beneficial effects of non-digestible carbohydrates and of the curative effects of anti-cancer drugs are sought. Furthermore, in Example 7 (page 12 of EP 0 692 252 A1) is mentioned that to determine potential synergistic therapeutic effects, a pharmaceutical composition comprising RAFTILINE® (i.e. chicory inulin) and a conventional chemotherapeutic product actively destroying malignant tumor cells, is prepared and a test is described wherein doxorubicine (an anti-cancer drug of the class of the antimitotic antibiotics) was injected to mice fed oligofructose/RAFTILINE® which were previously inoculated with L1210 leukaemic tumor cells. However, EP 0 692 252 A1 is completely silent about the outcome of the test and about possible synergistic effects between a non-digestible fructan-type carbohydrate and conventional anti-cancer drugs.

The combined effect of levan and four cytotoxic agents on the growth of experimental tumors in mice has been published (Leibovici et al., 1983). Additive effects were observed with all the combinations of levan and the cytotoxic agents, except for the combination of levan and methotrexate, an-

The composition according to the invention can be prepared by conventional methods, comprising, for example, mixing the desired amounts of the active components, optionally in combination with one or more pharmaceutically acceptable solvents, diluents, excipients, and/or additives commonly used in galenic pharmacy.

The compositions can be presented in conventional, well known galenic forms for oral, parenteral or rectal administration, or for tube feeding. The compositions for oral administration can for example be liquids, gels or solids and exist, for example, as tablets, coated tablets, coated pills, capsules, granules, solutions, syrups, suspensions or emulsions. The compositions for administration via tube feeding can for example be solutions, syrups, suspensions or emulsions which optionally can be mixed with normal food compositions for tube feeding. The compositions for rectal administration may for example be solids, gels or liquids, presented for example in the form of suppositories, gels, solutions, suspensions or emulsions. The composition for parenteral administration can for example be in the form of a solution, emulsion or suspension, suitable for said administration, including for subcutaneous, intramuscular, intraveneous and intraperitoneal administration.

Suitable galenic forms also include retard release forms as well as sustained release forms which are well known in the art.

The composition according to the invention comprises at least an effective dose of the inulin as well as of the anti-cancer drug or drug mixture. A dose which is effective for treatment of cancer can be formulated in the form of a single dose unit or of several partial dose units, the administration of which can be spread over a certain period of time. Usually the composition according to the invention will be administered spread over several partial dose units, and spread, possibly with certain intervals, over one or more days or weeks.

The effective dose of the synergistic combination of inulin and anti-metabolic anti-cancer drug may depend on various factors, including the affected being, a human or species of non-ruminating mammals, its age and physical condition, the kind and stage of development of the cancer, the kind of inulin and of anti-cancer drug, and the method of administration of the synergistic combination. The effective dose, the optimal galenic form and unit dose, and the way of administration can be determined by the skilled person following conventional methods.